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10/041,018	01/07/2002	Seiichi P.T. Matsuda	HO-P02080US1	2605

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,018	MATSUDA ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-79* is/are pending in the application.

4a) Of the above claim(s) *19-24 and 33-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *abstract*.

DETAILED ACTION

Status of the Application

Claims 1-79 are pending.

Applicant's election with traverse of (a) Group I, claims 1-18 and 25-32 drawn in part to a microorganism comprising exogenous nucleic acids encoding a geranylgeranylpyrophosphate synthase, a diterpene synthase, and HMG-CoA reductase, as well as a upc-2-1 polynucleotide, and (b) SEQ ID NO: 1, SEQ ID NO: 361, and SEQ ID NO: 383, in a communication filed on 9/29/2004 is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants submit in the response to the election/restriction requirement filed on 9/29/2004 that claims 19-24 and 33-79 have been cancelled without prejudice or disclaimer. It is noted however that no new listing of the claims indicating such cancellation has been found in the record. As such, the claims as shown in the listing of claims filed on 1/7/2002 are pending.

Claims 19-24 and 33-79 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

1. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/259,880 filed on 01/05/2001.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 7/9/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

3. Claims 2-3, 26-27, 30-31 are objected to because they are partially drawn to non-elected inventions. Examination of such claims will be restricted to the subject matter elected, which in the instant case is a microorganism comprising a polynucleotide encoding the polypeptide of SEQ ID NO: 22 (the polynucleotide of SEQ ID NO: 1) and a polynucleotide encoding the polypeptide of SEQ ID NO: 383 (the polynucleotide of SEQ ID NO: 361). Appropriate correction is required.

4. Claims 6, 9, 10, 13, 25, 29 are objected to due to the recitation of "ADH", "PGK", and "HMG-CoA". Abbreviations unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. It is suggested that the terms "alcohol dehydrogenase", "phosphoglycerine kinase", and "3-hydroxy-3-methylglutaryl-CoA" be recited at least once in the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-18 and 25-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 1, 4, 7, 10, 25, 29 (claims 2-3, 5-6, 8-9, 11-18, 26-28, 30-32 dependent thereon) are indefinite in the recitation of "nucleic acid sequence encoding.....under the control of a promoter", and "said promoter of said nucleic acid sequence encoding..." for the following reasons. As known in the art, nucleic acid sequences are graphical representations of the order in which nucleotides are assembled in a polynucleotide. Therefore, promoters control the expression of polynucleotides and not their sequences. For examination purposes, it will be assumed that the terms read "nucleic acid encoding.....under the

control of a promoter" and "said promoter of said nucleic acid encoding...". Correction is required. Should Applicants amend the claims such that the language indicated above is used, dependent claims may have to be amended to maintain the proper antecedent basis.

8. Claim 14 is indefinite in the recitation of "exogenous nucleic acid sequence that confers to said organism an increase in sterol metabolic flux..." as it is unclear how a sequence, which is a graphical representation as indicated above, can confer an organism an increase in sterol metabolic flux. For examination purposes, it will be assumed that the term reads "exogenous nucleic acid that confers to said organism an increase in sterol metabolic flux...". Correction is required.

9. Claim 25 is indefinite in the recitation of "upc2-1 nucleic acid sequence" for the following reasons. While the gene nomenclature used may be appropriate for S. cerevisiae since according to the specification, upc2-1 corresponds to an allele of the S. cerevisiae upc2p gene which encodes a transcription factor, the use of this nomenclature for genes encoding proteins of identical function in other organisms may not be accurate. As known in the art, genes encoding proteins of identical function in two different organisms may use different designations. For example, the ARO4 gene of Candida albicans encodes a DAHP synthase whereas the E. coli counterpart is the aroF gene. See the abstract of Sousa et al. (Microbiology 148(Pt5):1291-1303, 2002). As such, the use of gene terminology which is applicable to some organisms and not to others is confusing since the claims use this gene nomenclature with respect to any organism. For examination purposes, it will be assumed that the term reads "a nucleic acid encoding an sterol uptake control transcription factor". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-18, and 25-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 4-9, and 11-18 are directed to a unicellular organism which produces a genus of diterpenes, wherein said organism comprises exogenous nucleic acids encoding a genus of geranylgeranyl pyrophosphate synthases and a genus of diterpene synthases. Claim 2, as interpreted, is directed to the unicellular organism of claim 1 wherein the exogenous nucleic acid encoding the geranylgeranyl pyrophosphate synthase is the polynucleotide of SEQ ID NO: 1 (encodes the polypeptide of SEQ ID NO: 22). Claim 3, as interpreted, is directed to the unicellular organism of claim 1 wherein the exogenous nucleic acid encoding the diterpene synthase is the polynucleotide of SEQ ID NO: 361 (encodes the polypeptide of SEQ ID NO: 383). Claim 10 is directed to the unicellular organism of claim 1 with the added limitation that the organism comprises an exogenous nucleic acid encoding a genus of HMG-CoA reductases. Claims 25 and 28 are directed to a unicellular organism which produces a genus of diterpene precursors or diterpenes, wherein said organism comprises exogenous nucleic acids encoding a genus of geranylgeranylpyrophosphate synthases, a genus of diterpene synthases, a genus of HMG-CoA reductases, and a genus of sterol uptake control transcription factors. Claim 26 is directed to the unicellular organism of claim 25 wherein the exogenous nucleic acid encoding geranylgeranyl pyrophosphate synthase is the polynucleotide of SEQ ID NO: 1. Claim 27 is directed to the unicellular organism of claim 25 wherein the exogenous nucleic acid encoding the diterpene synthase is the polynucleotide of SEQ ID NO: 361. Claims 29 and 32 are directed to a unicellular organism which produces a genus of diterpene precursors or diterpenes, wherein said organism comprises exogenous nucleic acids encoding a genus of geranylgeranylpyrophosphate synthases, a genus of diterpene synthases, a genus of HMG-CoA reductases, and a genus of proteins which allow for an increase in sterol

metabolic flux. Claim 30 is directed to the unicellular organism of claim 29 wherein the exogenous nucleic acid encodes the geranylgeranyl pyrophosphate of SEQ ID NO: 22. Claim 31 is directed to the unicellular organism of claim 29 wherein the exogenous nucleic acid encodes diterpene synthase of SEQ ID NO: 383. See Claim Objections and Claim Rejections under 35 USC 112, second paragraph above for claim interpretation.

While the specification (1) discloses examples where an S. cerevisiae cell is modified such that it contains the S. cerevisiae upc2-1 allele (encodes a mutated upc2p transcription factor), and expresses the S. cerevisiae genes encoding geranylgeranyl diphosphate synthase (BTS1; SEQ ID NO: 22), HMG-CoA reductases, and abietadiene synthase (SEQ ID NO: 388) to produce abietadiene, and (2) indicates that the claimed organism can be modified such that it can express known genes in the art which encode geranylgeranyl pyrophosphate synthases, HMG-CoA reductases, and diterpene synthases, the claimed organisms require not only nucleic acids of those enzymes listed in the specification which are known in the art but they require nucleic acids encoding (a) unknown geranylgeranyl pyrophosphate synthases, HMG-CoA reductases, diterpene synthases, sterol uptake control transcription factors, and (b) proteins of unknown structure and function which can increase the sterol metabolic flux. Furthermore, the claims require the production of any diterpene/diterpene precursor with a host cell comprising nucleic acids encoding any geranylgeranyl pyrophosphate synthase, diterpene synthase, and HMG-CoA reductase. The specification fails to disclose (1) the critical structural elements required in a gene encoding any geranylgeranyl pyrophosphate synthase, HMG-CoA reductase, and diterpene synthase, (2) the critical structural elements required in any gene encoding any sterol uptake control transcription factor or a corresponding allele which would allow for increased sterol uptake, (3) the critical structural elements required in any polynucleotide such that it encodes a polypeptide which would allow an increase in sterol metabolic flux, and (4) which diterpenes and diterpene precursors can be made with the infinite number

of combinations of geranylgeranyl pyrophosphate synthases, HMG-CoA reductases, and diterpene synthases required to be produced by the claimed organism.

Each of the genus of polynucleotides required to make the claimed organism is a large, structurally variable genus. While a sufficient written description of a genus of polynucleotides may be achieved by a recitation of a representative number of polynucleotides defined by their nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus., in the instant case, there is no structural feature which is representative of all the members of the genus of polynucleotides recited in the claims. Furthermore, while one could argue that the recited genus of polynucleotides is adequately described by those polynucleotides disclosed in the specification and those known in the art since one could use structural homology, it is noted that the art teaches the unpredictability of using structural homology to accurately determine function and even a high degree of structural homology may not result in functional homology. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β–ketoacyl synthase into a malonyl decarboxylase and completely eliminates β–ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Therefore, in the absence of any additional information correlating structure with each of the functions recited, many structurally unrelated polynucleotides are encompassed by the genus. The specification discloses a few species of each of the genus of polynucleotides required, genus, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within each of the genus of polynucleotides required to make the claimed organism. Therefore, one skilled in the art

cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

12. Claims 1-18, and 25-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (a) a unicellular organism for producing abietadiene and abietadiene precursors wherein said organism comprises the polynucleotide of SEQ ID NO: 1 (S. cerevisiae BTS1 gene), the polynucleotide of SEQ ID NO: 365 (encoding the Abies grandis abietadiene synthase of SEQ ID NO: 388), and the S. cerevisiae hmg1p gene encoding HMG-CoA, and (b) a S. cerevisiae host cell comprising the polynucleotide of SEQ ID NO: 1, the polynucleotide of SEQ ID NO: 365, the S. cerevisiae hmg1p gene, and the upc2-1 allele of the S. cerevisiae upc2p gene, does not reasonably provide enablement for (1) a unicellular organism for producing any diterpene or diterpene precursors wherein said organism comprises a polynucleotide encoding any geranylgeranylpyrophosphate synthase and any diterpene synthase, (2) the organism of (1) further comprising a polynucleotide encoding any HMG-CoA reductase, (3) the organism of (2) further comprising a polynucleotide encoding any sterol uptake control transcription factor, (4) the organism of (2) further comprising a polynucleotide encoding a polypeptide which increases sterol metabolic flux, or (5) a unicellular organism for producing any diterpene or diterpene precursor wherein said organism comprises the polynucleotide of SEQ ID NO: 1 and the polynucleotide of SEQ ID NO: 361 (encoding a Stevia rebaudiana kaurene synthase). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6)

the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims, as described above, is not commensurate with the enablement provided in view of the large number of polynucleotides of unknown structure encoding the proteins required to make the claimed organisms, and the unknown diterpene/diterpene precursors which can be made with any combination of geranylgeranylpyrophosphate synthases, diterpene synthase, and HMG-CoA reductases, as required in the claims. While some of the polynucleotides required have been disclosed either in the specification or the prior art, there is no disclosure of (1) all the other polynucleotides required in the claimed organism, (2) the structural features common to all the polynucleotides recited such that they encode proteins with the desired function, (3) the critical structural elements in the polynucleotides of SEQ ID NO: 1, 361, 365, the S. cerevisiae hmg1p gene, and the upc2-1 allele of the S. cerevisiae upc2p which are required such that they encode proteins having the required function, and (4) the specific diterpene/diterpene precursors which can be made with any combination of geranylgeranylpyrophosphate synthases, diterpene synthase, and HMG-CoA reductases, as recited in the claims. It is noted that while the specification discloses how to make abietadiene (diterpene) by transforming a S. cerevisiae cell comprising a polynucleotide encoding the S. cerevisiae BTS1 gene (SEQ ID NO: 1), the polynucleotide of SEQ ID NO: 365 (encodes the Abies grandis abietadiene synthase of SEQ ID NO: 388), the S. cerevisiae hmg1p gene encoding HMG-CoA, and the S. cerevisiae upc2-1 allele of the upc2p gene, the specification is silent in regard to other diterpenes which can be made with said transformed S. cerevisiae, or which diterpene/diterpene precursor can be made with a host cell comprising the polynucleotides of SEQ ID NO: 1 and SEQ ID NO: 361 (encodes the Stevia rebaudiana kaurene synthase of SEQ ID NO: 383). While one could argue that an organism transformed with the polynucleotide of SEQ ID NO: 1 and the polynucleotide of SEQ ID NO: 361 would allow the formation of kaurene (diterpene) since the polynucleotide of SEQ ID NO: 361 encodes a kaurene synthase, it is

noted that Richman et al. (The Plant Journal 19(4):411-421, 1999) teaches that the conversion of geranylgeranyl diphosphate to kaurene requires the intermediate copalyl diphosphate, which is formed in a reaction catalyzed by a copalyl diphosphate synthase (page 412, Figure 1). Thus, even if one were to transform any host cell with the polynucleotides of SEQ ID NO: 1 and 361, it is unclear as to how one can produce any diterpene or kaurene if there is no expression of the required copalyl diphosphate synthase.

The art as discussed above, teaches the unpredictability of accurate function assignment based solely on structural homology and indicates that even high structural homology does not always results in functional homology. Since structure determines function, one of skill in the art would require some knowledge or guidance as to which are the structural elements in a polynucleotide which are characteristic and required such that they encode proteins having the desired function. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required in a polynucleotide such that it encodes a polypeptide displaying the desired function, the lack of knowledge as to which specific diterpenes and/or diterpene precursors can be made with any combination of geranylgeranylpyrophosphate synthases, diterpene synthase, and HMG-CoA reductases, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to screen and isolate those polynucleotides required in the claimed organism, and determine which diterpene/diterpene precursor can be made with the claimed organism. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Conclusion

13. No claim is in condition for allowance.

14. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
November 7, 2004

REBECCA E. PROUTY
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